

# 건강한 한국 성인에서 비타민 D 농도와 내장지방면적의 상관관계

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## Association between Vitamin D Concentration and Visceral Fat Area in Healthy Korean Adults

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**Background:** Studies on the relationship between vitamin D and visceral fat area (VFA; intra-abdominal fat area) have been actively conducted. But, there is a few Korean population-based studies about the association between serum vitamin D level and VFA. The aim of our study was to explore the correlation between serum 25-hydroxyvitamin D (25[OH]D) levels and VFA measured using bioelectrical impedance analysis (BIA; electric impedance) in healthy Korean adults.

**Methods:** This cross-sectional study involved 1,945 adults aged 20-70 years who visited a health promotion center. All subjects underwent the BIA to estimate the VFA. Serum 25(OH)D level was measured using chemiluminescent immunoassay. Multiple regression analysis was performed to identify independent correlation of VFA and serum 25(OH)D level.

**Results:** The prevalence of vitamin D deficiency (25[OH]D: 20-29 ng/mL) and insufficiency (25[OH]D <20 ng/mL) were 54.4% and 38.1%, respectively. After having adjusted age and season, VFA were negatively associated with serum 25(OH)D levels in both men ( $P<0.001$ ) and women ( $P<0.001$ ). The obese group with VFA  $\geq 100 \text{ cm}^2$  had significant lower serum 25(OH)D level in men ( $P<0.001$ ) and women ( $P=0.0034$ ).

**Conclusions:** VFA measured using BIA could be negatively associated with serum 25(OH)D levels in healthy Korean adult.

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**Keywords:** Vitamin D, Intra-abdominal fat, Electric impedance, Obesity

### Introduction

In the past, it has been demonstrated that vitamin D is an essential nutrient of bone metabolism and calcium homeostasis.<sup>1)</sup> In recent years, it has become clearer that vitamin D has additional physiological functions by cell signaling and regulating gene expression.<sup>2)</sup> Several studies have

reported that vitamin D deficiency affects obesity-related metabolic disease including diabetes, cardiovascular disease, and moreover autoimmune disease and cancer.<sup>3,4)</sup>

In this context, the relationship between obesity, which is being recognized as a major global public health problem, and vitamin D is interestingly evaluated. Several cross-sectional study and meta-analysis have reported that blood vitamin D concentration is negatively correlated with obesity indicators, such as body weight, body mass index (BMI), percentage body fat (PBF), visceral adipose tissue (VAT).<sup>5,6)</sup> The risk of metabolic diseases appears based on different region of body fat accumulates, especially, visceral adiposity seems to have a closer relationship than another anthro-

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pometric indicator.<sup>7)</sup> On that basis, researches for the relationship between visceral fat and vitamin D are actively discussed and studied. Our study is to explore the correlation between visceral fat area (VFA) and vitamin D in healthy Korean adults, using bioelectrical impedance analysis (BIA) as a simple and inexpensive method for measure of VFA.

## Methods

### 1. Subjects

This retrospective cross-sectional study based on data extracted from the medical records. We enrolled 2,881 subjects coming to the Health Promotion Center, for routine health check-up during April to December in 2016. A total of 1,945 subjects (1,395 men and 550 women) were included for analysis according to the following eligibility criteria. Inclusion criteria were as follows: 1) age of 20-70 years, 2) individuals who measured serum 25-hydroxyvitamin D (25[OH]D) concentration and conducted BIA. Exclusion criteria were as follows: 1) individuals with BMI less than 18.5 kg/m<sup>2</sup>, 2) with kidney or liver disease, 3) with diabetes, inflammatory bowel disease and absorptive disease, 4) with thyroid or parathyroid disease, 5) with malignancy, psychiatric disease, and 6) with history of organ transplantation. Demographic information containing age, gender, height, weight, smoking behavior, alcohol behavior, past medical history and medication history was obtained from a standardized questionnaire. This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the Inje University Sanggye Paik Hospital (IRB No. 2017-06-029).

### 2. Laboratory measurements

All blood samples were taken after at least 12 hour-fasting. Total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), fasting glucose were measured using dedicated reagents by automatic chemistry analyzer (AU 5400; Beckman-Coulter, Fullerton, CA, USA). Serum 25(OH)D levels were measured using chemiluminescent immunoassay (Advia Vitamin D Total assay; Siemens Healthcare, Erlangen, Germany).

### 3. Anthropometric and body fat measurements

Anthropometric measurement was taken after at least 12 hour-fasting with subjects wearing light robe and no shoes. Weight and height were measured to the nearest 0.1 kg and 0.1 cm each other using an automatic scale (BSM330; Biospace, Seoul, Korea). Body mass index was calculated as weight in kilograms divided by height in meters squared. VFA and PBF were estimated by the bioelectrical impedance analysis (BIA) method (Inbody770; Biospace). There is a diversity of references regarding on range of blood vitamin D levels. In the current study, a serum level of 25(OH)D <20 ng/mL is defined as vitamin D deficiency, whereas a level 20-29 ng/mL is insufficient, and a level ≥30 ng/mL is sufficient.<sup>8)</sup> Obesity was defined as a BMI value exceeding 25 kg/m<sup>2</sup>.<sup>9)</sup> Or obesity was defined as PBF ≥25% in men and PBF ≥30% in women.<sup>10)</sup> Visceral fat obesity was defined as a VFA exceeding 100 cm<sup>2</sup>.<sup>11)</sup>

### 4. Statistical analyses

Continuous variables are expressed as means±standard deviation, categorical variables were presented as a total number (percentage). The subgroup comparisons between the men and women group were tested using independent-sample *t*-test. Pearson correlation analysis was performed to analyze the relationships between serum 25(OH)D and other variables. Multiple regression analysis was performed to identify independent correlations of obesity-related variables and serum 25(OH)D levels. Participants were divided into obese and non-obese group according to their obesity-related variables, the subgroup comparisons in serum vitamin D status between obese and non-obese group were conducted using independent-sample *t*-test. The local-weighted scatterplot smoothing models (Loess) was used to explore the association between obesity-related variables and serum 25(OH)D levels of gender- and age-group. Loess is a nonparametric method for fitting a smooth curve between two variables, which was performed in R statistical package (R version 3.2.5). Statistical analysis was performed by SPSS statistical software version 19.0 (IBM Corp., Armonk, NY, USA). A *P*-value <0.05 was regarded as statistically significant.

## Results

### 1. The characteristics of the study subjects

The characteristics of the subjects were shown in Table 1. The prevalence of vitamin D deficiency was higher in women (66%) than in men (49.9%), while the prevalence of vitamin D insufficiency was higher in men (42.7%) than in women (26.5%). In the case of sufficient vitamin D level, prevalence was shown similar in men (7.4%) and in women (7.5%). The prevalence of obesity based on BMI was higher in men (46.5%) than in women (25.6%), while the prevalence of obesity based on PBF was higher in women (72.2%) than in men (43.7%). In the case of high VFA level, prevalence was discovered higher in women (38.2%) than in men (16.8%). There was significant difference in BMI, PBF, VFA, systolic blood pressure, diastolic blood pressure, serum 25(OH)D, TG, HDLC, LDLC, fasting glucose. However, there was no difference in age ( $P=0.204$ ) and total cholesterol ( $P=0.916$ ) between the men and women.

### 2. Relation analysis of vitamin D and obesity-related variables

To evaluate the variables associated with serum 25(OH)D levels, correlation analysis was conducted (Table 2). Serum 25(OH)D levels had negative association with VFA, BMI, PBF, TG in both men and women, whereas age had positive association. Serum 25(OH)D levels was negatively associated with systolic and diastolic blood pressure, total cholesterol, fasting glucose only in men. Serum 25(OH)D levels was positively associated with HDLC only in men, serum 25(OH)D levels was positively associated with LDLC only in women. Changes of serum 25(OH)D levels according to their obesity-related variables between the obese and non-obese groups (Figure 1). The non-obese groups divided by BMI and VFA presented a higher serum 25(OH)D levels in both men and women. Although the non-obese group divided by PBF exhibited a significantly higher serum 25(OH)D levels only in men.

### 3. Regression analysis

After having adjusted age and season, BMI, PBF, VFA

**Table 1.** Characteristics of study subjects

	Total (n=1,945)	Men (n=1,395)	Women (n=550)	$P^a$
Age (y)	46±9.5	46.3±9.1	47±10.4	0.204
BMI (kg/m <sup>2</sup> )	24.6±3.2	25±3	23.3±3.2	<0.001
Normal (18.5-22.9)	639 (32.9)	346 (24.8)	293 (53.3)	<0.001
Overweight (23-24.9)	517 (26.6)	401 (28.7)	116 (21.1)	0.001
Obese (≥25)	789 (40.6)	648 (46.5)	141 (25.6)	<0.001
Percentage body fat (%)	27±8	24.4±5.4	33.1±5.8	<0.001
Non-obese (<25 in males, <30 in females)	939 (48.3)	786 (56.3)	153 (27.8)	<0.001
Obese (≥25 in males, ≥30 in females)	1,006 (51.7)	619 (43.7)	397 (72.2)	<0.001
VFA (cm <sup>2</sup> )	82.5±31.7	78±29	94.1±10.4	<0.001
Normal (<100)	1,501 (77.2)	1,161 (83.2)	340 (61.8)	<0.001
High-VFA (≥100)	444 (22.8)	234 (16.8)	210 (38.2)	<0.001
Blood pressure (mmHg)				
Systolic	118.5±13.9	120.4±13.2	113.4±14.4	<0.001
Diastolic	78.4±11.3	80.1±11.1	74.3±10.9	<0.001
25(OH)D (ng/mL)	19.5±7.4	20.3±7	17.3±8	<0.001
Normal (≥30)	144 (7.4)	103 (7.4)	41 (7.5)	0.957
Insufficiency (20-29.9)	742 (38.1)	596 (42.7)	146 (26.5)	<0.001
Deficiency (<20)	1,059 (54.4)	696 (49.9)	363 (66)	<0.001
Total cholesterol (mg/dL)	193.4±34.8	193.4±35	193.6±34.4	0.916
Triglyceride (mg/dL)	138.9±91	153.1±98.3	102.8±54	<0.001
HDL cholesterol (mg/dL)	50.7±11.8	48.2±10.3	57.1±13.1	<0.001
LDL cholesterol (mg/dL)	119.2±25.6	120.4±25.7	116.2±25.3	0.001
Fasting glucose (mg/dL)	87.2±10.4	88.1±10.6	84.8±9.8	<0.001

Abbreviations: BMI, body mass index; VFA, visceral fat area; 25(OH)D; 25-hydroxyvitamin D; HDL, high density lipoprotein; LDL, low density lipoprotein.

Variables are presented as mean±standard deviation or number (%).

<sup>a</sup> $P$ -value from an independent-sample  $t$ -test for continuous variables and  $\chi^2$  test for categorical variables.

**Table 2.** Correlation between serum 25(OH)D and variables

	Men		Women	
	<i>r</i> <sup>a</sup>	<i>P</i> <sup>b</sup>	<i>r</i>	<i>P</i>
Age	0.142	<0.001	0.305	<0.001
Body mass index	-0.127	<0.001	-0.134	0.002
Percentage body fat	-0.195	<0.001	-0.096	0.025
Visceral fat area	-0.185	<0.001	-0.153	<0.001
Systolic blood pressure	-0.079	0.003	-0.038	0.379
Diastolic blood pressure	-0.115	<0.001	-0.064	0.133
Total cholesterol	-0.087	0.001	0.060	0.160
Triglyceride	-0.312	<0.001	-0.163	<0.001
High density lipoprotein cholesterol	0.058	0.031	0.006	0.892
Low density lipoprotein cholesterol	-0.029	0.284	0.105	0.014
Fasting glucose	-0.062	0.020	-0.029	0.493

Abbreviation: 25(OH)D, 25-hydroxyvitamin D.

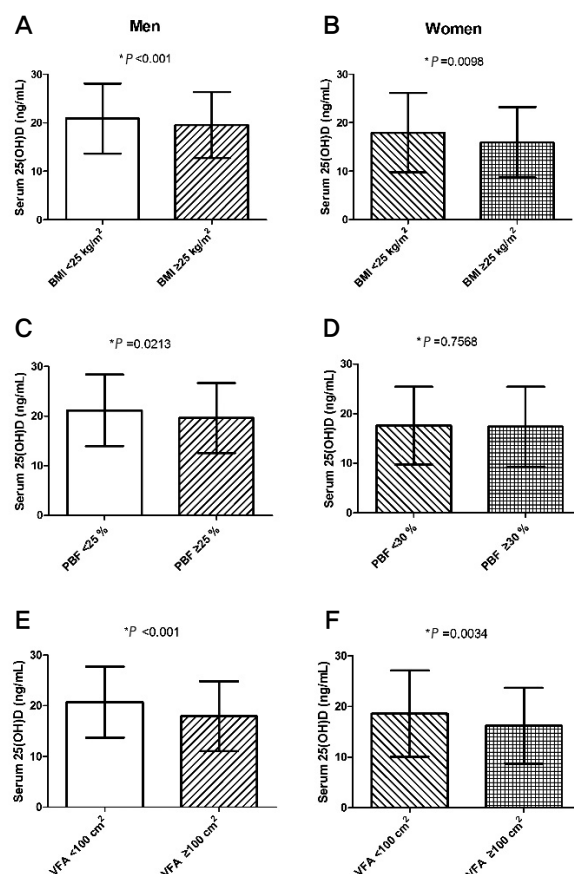
<sup>a</sup>Correlation coefficients.<sup>b</sup>*P*-value are calculated by Pearson correlation analysis.

were negatively associated with serum 25(OH)D levels in the multiple regression analysis (Table 3). The Loess smoothing curves overall appeared that serum 25(OH)D levels tend to decrease with increasing obesity-related variables gene, in some cases, which shown different slope according specific part of curves (Figure 2). Serum 25(OH)D level presented consistent decrease according with increasing BMI in men, radical decrease was observed in women at the range of BMI over 25 kg/m<sup>2</sup>. Serum 25(OH)D level represented decreasing trend at the range of VFA under 100 cm<sup>2</sup> and over 100 cm<sup>2</sup> in men and women respectively. Serum 25(OH)D level presented decrease according with increasing PBF all over the scales in men, decrease was observed only at the range of PBF over 35% in women. Serum 25(OH)D level presented decrease according with increasing VFA all over scales in women over 50 years, decrease was observed only at the range of with VFA over 100 cm<sup>2</sup> in women under 50 years old.

## Discussion

South Korea is one of the countries which has a high prevalence of vitamin D deficiency or insufficiency,<sup>12)</sup> furthermore, lifestyle is gradually changing into fewer outdoor activities during the daytime. Nevertheless, there are fewer domestic researches on relationship between vitamin D level and obesity. The aim of our study was to evaluate the association serum vitamin D levels and obesity-related variables, especially VFA.

**Figure 1.** Differential serum 25-hydroxyvitamin D (25[OH]D) concentrations in subjects with or without obesity. (A, B) Comparison of serum 25-hydroxyvitamin D (25[OH]D) levels according to body mass index (BMI) in men and women. Subjects with a BMI  $\geq 25$  kg/m<sup>2</sup> were classified as obese. (C, D) Comparison of serum 25(OH)D levels according to percentage body fat (PBF) in men and women. Men with a PBF  $\geq 25$  % and women with a PBF  $\geq 30$  % were classified as obese. (E, F) Comparison of serum 25[OH]D levels according to visceral fat area (VFA) in men and women. Subjects with a VFA  $\geq 100$  cm<sup>2</sup> were classified as obese. Data are presented as mean $\pm$ standard deviation. \**P* value from an independent-sample *t*-test.



We analyzed men and women separately due to difference in distribution of body fat between men and women. The results of the correlation analysis and multiple regression analysis indicated that BMI, PBF, VFA were negatively associated with serum 25(OH)D levels in men and women. There is a significant high levels of serum vitamin D in non-obese groups as compared to the obese groups, except for the case of women with PBF  $<30\%$ . In existing studies, researches have reported inconsistent outcomes on association between blood vitamin D levels and obesity-re-

**Table 3.** Regression analysis of relationship between vitamin D and obesity indices

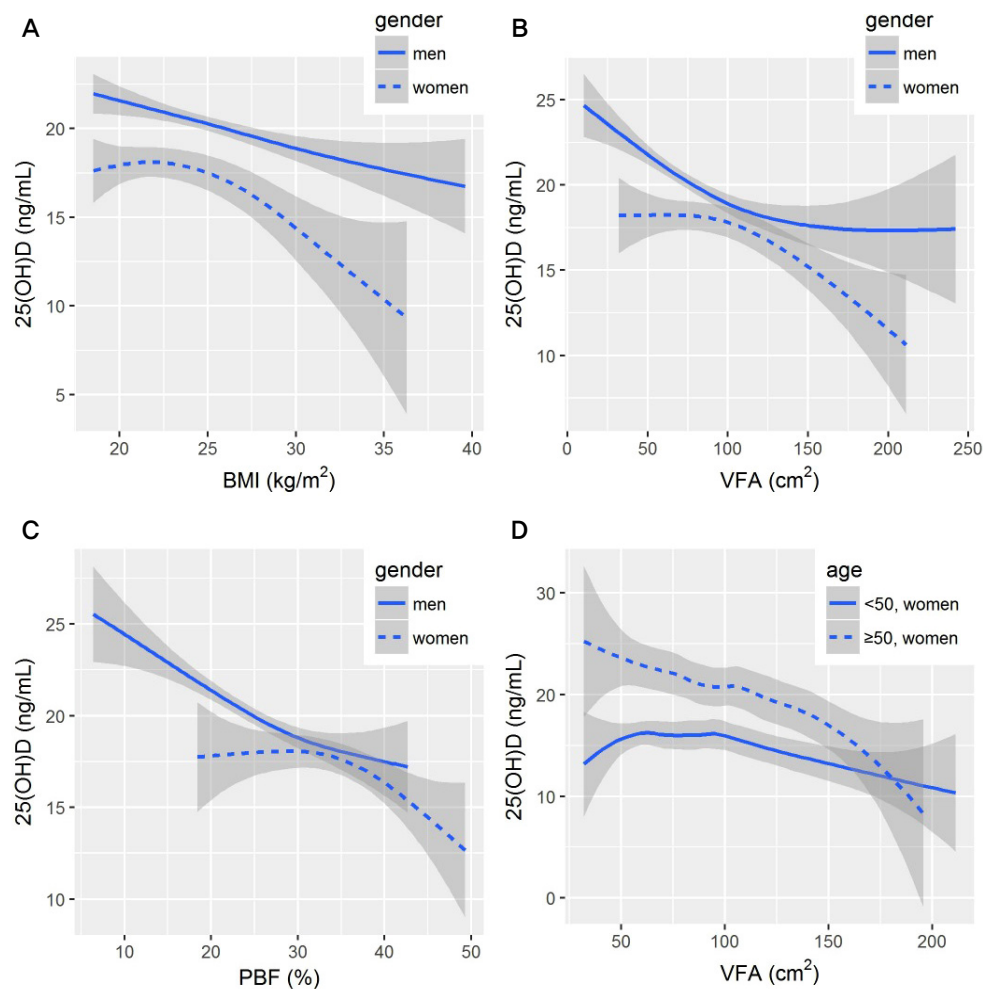
	Men		Women	
	$\beta \pm \text{SE}$	$P^a$	$\beta \pm \text{SE}$	$P$
Model 1 <sup>b</sup>				
Body mass index	-0.004 $\pm$ 0.064	0.950	-0.342 $\pm$ 0.111	0.002
Percentage body fat	-0.142 $\pm$ 0.035	<0.001	-0.158 $\pm$ 0.059	0.008
Visceral fat area	-0.018 $\pm$ 0.007	0.008	-0.034 $\pm$ 0.010	-0.149
Model 2 <sup>c</sup>				
Body mass index	-0.188 $\pm$ 0.060	0.002	-0.492 $\pm$ 0.100	<0.001
Percentage body fat	-0.211 $\pm$ 0.033	<0.001	-0.225 $\pm$ 0.056	<0.001
Visceral fat area	-0.032 $\pm$ 0.006	<0.001	-0.046 $\pm$ 0.009	<0.001

Abbreviation: SE, standard error.

<sup>a</sup> $P$ -value are calculated by multiple regression analysis.

<sup>b</sup>Model 1 was adjusted for age, SBP, DBP, total cholesterol, TG, HDL-C, LDL-C, glucose and season.

<sup>c</sup>Model 2 was adjusted for age and season. Model 2 was final model.

**Figure 2.** Correlation between 25(OH)D and fatness indices in men and women (A-C); in women aged  $\geq 50$  and  $< 50$  years (D). Smoothing curve with 95% confidence interval (shaded areas) are fitted by a Loess curve.

Abbreviations: Loess, local-weighted scatterplot smoothing models; 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; VFA, visceral fat area; PBF, percentage body fat.

lated variables. Majority of studies was reported that obesity-related variables, such as, weight, waist circumference, BMI, PBF, visceral adipose tissue have negative correlation with blood vitamin D levels.<sup>13-15)</sup> In several studies, VFA showed significant correlation with blood vitamin D levels, although weight, waist circumference but not BMI.<sup>16,17)</sup>

As vitamin D binding proteins (VDR) are discovered in many tissues, it has been identified that vitamin D affects various medical conditions. VDR play a role in various biological responses, such as, cell proliferation-inhibition, cell maturation and immune system.<sup>18)</sup> To explain why vitamin D deficiency occurs in obese population, the following mechanisms have been suggested: 1) less sunlight exposure due to less activity, 2) reduced vitamin D synthetic capacity, 3) sequestration of vitamin D in adipose tissue, and 4) dilution effect by quantitative increase.<sup>19)</sup> Several mechanisms have been suggested to explain the role of vitamin D in obesity, but it is not clear yet, which include: 1) Increased levels of parathyroid hormone in vitamin D deficiency, that can increase lipogenesis by overflow of calcium into adipocytes,<sup>20)</sup> 2) Decreased leptin synthesis due to depletion of vitamin D, that may increase appetite and lead to obesity.<sup>21)</sup> Vitamin D deficiency less than 20 ng/mL (50 nmol/L) had significant correlation with occurrence of obesity in the cohort study of 2,460 Norwegian subjects.<sup>22)</sup> A meta-analysis presented that vitamin D supplement did not improve obesity-related variables,<sup>23,24)</sup> whereas other meta-analysis presented that blood vitamin D levels increase as weight or PBF decreases.<sup>25)</sup>

Sun et al.<sup>16)</sup> demonstrated that serum vitamin D levels are negatively correlated with VFA using magnetic resonance imaging (MRI), which is in correspond with outcome of our study, But not BMI. Shin et al.<sup>17)</sup> found that 25(OH)D is negatively correlated with visceral adipose tissue using and is not associated with waist circumference and BMI. These findings were partially similar to the results of our study. Kim and Kim<sup>26)</sup> suggested that 25(OH)D is associated with adiposity but not with the indicators used to estimate adiposity, such as waist circumference or BMI. These findings were inconsistent with our outcomes that BMI, PBF, VFA estimated by BIA were associated with 25(OH)D. Most of previous studies used sophisticated methods to estimate of the amount of adipose tissue, such as computed tomography (CT), dual-energy x-ray absorptiometry (DEXA) and MRI. Above mentioned imaging mo-

dalities are precise, but expensive or higher risk related to radiation. BIA is modality to assess body composition from differences of tissue conductivity. Existing studies demonstrated that BIA accurately estimate body fat and VFA.<sup>27-29)</sup> Nagai et al.<sup>27)</sup> reported that VFA measured using BIA is strongly correlated with CT-measured VFA ( $r=0.905$ ,  $P<0.01$ ). BIA is considered useful method to measure adiposity, relatively less expensive, less exposed to radiation and easier. In our knowledge, researches of association between blood vitamin D levels and VFA measured using BIA are few and none of domestic research exists.

The strength of our study is to evaluate the relationship between serum 25(OH)D and VFA in a large number of Korean healthy subjects and use BIA, which is easier, less expensive and less risk of radiation, to measure VFA. Whereas there are several limitations. First, we could not reveal the causal relationship between vitamin D and VFA, because this study was a cross-sectional study. Second, the results of this study could not be generalized because there may be selection bias in that only healthy adults who visited the Health Promotion Center were enrolled. Third, self-reporting questionnaire precluded from taking complete demographic data. Information on menopausal status and vitamin D supplementation as mentioned above, drinking, smoking and degree of sunlight exposure was incomplete and unreliable. Therefore, prospective studies should be conducted on more populations in the future.

Zhang et al.<sup>30)</sup> discovered that higher VFA increases the risk of vitamin D deficiency and insufficiency in men and pre-menopausal women, but not in post-menopausal women. In our study, we could not have a reliable information about menopausal status owing to limitations of self-reporting questionnaire, accordingly, women were grouped into two based on the age of 50 instead of menopausal status. (Figure 2D) In our study, serum vitamin D level reduces as VFA increases in women over 50 years old, menopause or impending. In this regard, there are disagreement with the results of above-mentioned. A relative small number of women, lack of information about menopausal status and vitamin D supplement are considered to be a cause of these disagreement. Thus, much more research remains to be done to further understand difference in the correlation of VFA and vitamin D status between post- and premenopausal women.

Interestingly, in the smooth curve fitted by Loess shown

different patterns of the shape and slope of the curves between men and women. Furthermore, the points of inflection on curves almost matched with existing reference points of obesity. To determine the cutoff point of obesity-related variable for assessing risk of vitamin D deficiency or insufficiency, more research is needed.

In conclusion, VFA measured using BIA could be negatively correlated with serum 25(OH)D levels in healthy Korean adult. VFA measured using BIA is expected to be a convenient biomarker for assessing risk of vitamin D deficiency or insufficiency in routine health check-up in the near future, more needs to prospective researches on large of subjects.

## 요약

**연구배경:** 비타민 D와 내장지방의 상관관계에 대한 연구가 활발히 이루어지고 있으나, 국내 연구는 많지 않은 실정이다. 본 연구는 건강한 한국인 성인에서 혈청 비타민 D 농도와 생체 전기 저항 측정법으로 측정된 내장지방면적 사이의 연관성에 대해 알아보려고 하였다.

**방법:** 본 단면연구는 건강증진센터를 방문한 20-70세의 1,945명의 성인을 대상으로 하였다. 모든 대상자에서 생체 전기 저항 측정법으로 내장지방면적을 추정하고, 화학발광면역 분석법으로 혈청 25-hydroxyvitamin D (25[OH]D) 농도를 측정하였다. 다중회귀분석을 시행하여 내장지방면적과 혈청 25(OH)D의 독립적인 상관관계를 확인하였다.

**결과:** 비타민 D 결핍(25[OH]D: 20-29 ng/mL)과 부족(25[OH]D <20 ng/mL)의 유병률은 각각 54.4%와 38.1%였다. 나이와 계절을 보정한 후, 내장지방면적은 남성( $P<0.001$ ) 및 여성( $P<0.001$ )에서 혈청 25(OH)D 농도와 음의 상관관계를 보였다.

**결론:** 건강한 한국인 성인에서 생체 전기 저항 측정법으로 측정된 내장지방면적과 혈청 25(OH)D 농도는 음의 상관관계를 보였다.

**중심 단어:** 비타민 D, 내장지방면적, 생체 전기 저항 측정법, 비만

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